in claims 30 and 31, and to the use of the term "specifically interferes" in claims 15 and 32.

With the cancellation of claims 1-35 and substitution of new claims as presented in the Listing of the Claims, Applicants submit that these rejections are moot. The stated terms have not been used in the new claims and more defined language has been employed.

Claims 1-34 were rejected under 35 U.S.C.§112, first paragraph as enabled only for a GIP antagonist comprising amino acids 7-30 or 10-30 of GIP but not to an antagonist that corresponds to a GIP sequence, one that comprises an effective number of amino acids in relation to a referenced sequence, effective alternative sequences or sequences comprising positions at 16-30, 21-30, 31-44 or 7-9 of GIP. In noting that only two of the sequences tested, 10-30 and 7-30, are shown effective, the Action alleges that undue trial and error would be necessary in order to identify additional antagonists. Additionally, the Action has taken the position that predicting structure and related function from primary amino acid sequence data is complex and not amenable to algorithmic analysis. In summary, the breadth of the claims is purportedly not justified to the extent there is limited guidance for making and using alternative sequences in the specification.

While not concurring with the basis for the Action's rejections, Applicants have submitted a new set of claims focused on particular structures that clearly meet requirements for enablement, written description and utility.

Applicants do not agree that in this particular case, the skilled artisan would not be able to identify key structural characteristics and, without undue experimentation, prepare variants of the sequences demonstrated to have GIP antagonist activity. The polypeptides shown to be active, in conjunction with those that lacked activity, indicate what primary structure would be expected to confer activity. As was pointed out on page 7-8 of the Office Action, it appears that the segment of amino acids from 10-30 GIP includes amino acids important for GIP antagonist activity.

The ordinary skilled artisan has more than a mere speculation of what to prepare and test. The 10-30 GIP segment can be readily used to make variants that are expected to be active. Practitioners are quite familiar with equivalent substitutions; *e.g.*, substitution of one neutral amino acid for another without noticeable change in biological or physical properties. Thus Applicants are justified in claiming equivalent substitutions at positions in the demonstrated active segments.

In fact, rat and human GIP have the same function, differing only in a single amino acid at position 18 of SEQ ID NO:2. The difference is his/arg, each considered an equivalent to the other. This is support for the different equivalent substitutions claimed by Applicants in the 7-30 and 10-30 GIP amino acid segments.

The comparable rat/human GIP activity also supports a claim to a 95% identity to the 7-30 and 10-30 GIP segments because of the single difference between rat and human GIP. GIP is a short 42 amino acid molecule. The skilled artisan, as taught in the specification, would not need to make an undue number of analogs of the 7-30 and 10-30 GIP segments, recognizing that other than equivalent substitutions, only a limited number of changes would be tolerated in order to maintain some GIP antagonist activity, which is readily determined by the tests set forth in the specification.

Accordingly, Applicants submit that the newly presented claims are enabled and that the claimed species do not require undue experimentation. Any number of amino acid segments (selected based on the guidance and teachings in the specification) comprising contiguous sequences of GIP would reasonably be within the scope of the invention.

In support of its position, the Action has drawn attention to the 1991 *Amgen v. Chugai* case. In that case, the proponents claimed a DNA sequence that encodes a polypeptide having a sequence sufficiently duplicative of EPO so that it had specified biological properties. Applicants maintain that there are important differences between this case and the claims currently presented. First, Applicants are not claiming a nucleic acid.

More importantly, the encoded EPO disclosed in the *Amgen* case is 165 amino acids in length. GIP is only 42; moreover, Applicants have focused on a segment of 24 amino acids in length. This, in combination with knowledge of equivalent substitutions, will limit the number of useful alternative sequences and therefore not require undue experimentation to prepare and test. Applicants submit that the new claims are not unduly broad.

The claims directed to preventing, inhibiting or reducing obesity have been rejected as lacking enablement. Applicants acknowledge the Action's recognition that the specification is enabling for reducing glucose adsorption. The specification on page 9, beginning at line 7, states that because a GIP receptor antagonist inhibits, blocks or reduces glucose absorption from the intestine, therapeutic compositions containing GIP antagonists may be used in patients with noninsulin dependent diabetes to improve glucose tolerance or to reduce obesity. The compositions, as currently presented, would be expected to reduce obesity. Attention is directed to a recent article in C&E News on page 60, middle column where a GLP-1 (another gastroregulatory peptide) based drug is "intended to manage blood glucose levels while encouraging weight loss and avoiding the risk of hypoglycemia." While this is a 2004 article, Applicants believe this is confirmation of the long-recognized nexus between intestinal glucose adsorption and preventing, inhibiting or reducing obesity. For the Examiner's convenience, Applicants attach a copy of the C&E News article. (Exhibit A)

All currently pending claims stand rejected under 35 U.S.C.§112, first paragraph as lacking written description. As discussed above, Applicants believe that the new set of claims provides a clearer description of the compositions employed and the properties or attributes of the different segments that are expected to have the claimed activity. It is believed that the metes and bounds of the number of amino acid substitutions and/or insertions/deletions do not unduly expand the scope of the variants that may be employed. As previously discussed, the skilled artisan is able from the guidance in the specification to prepare and use additional GIP antagonists without undue

experimentation based the species disclosed as working examples and the level of skill in the art.

REJECTION UNDER 35 U.S.C.§101

Claim 10 has been rejected as failing to fall within a statutory class of invention. Applicants have canceled this claim, thereby rendering this rejection moot.

DOUBLE PATENTING

Claims 1-34 are provisionally rejected under 35 U.S.C.§101 for claiming the same invention as claims 1,8-16 and 18-41 in copending application Serial Number 08/984,476.

Applicants respectfully request the opportunity to respond to this rejection at such time as any conflicting claims in earlier filed application may be allowed, as claims in either application may undergo amendments making the rejection inappropriate.

Claim 1-34 have also been provisionally rejected under the judicially created doctrine of obviousness-type double patenting as unpatentable over claims 1, 8-16, and 18-41 of copending application 08/984,476. The claims are stated not to be identical and if maintained in view of allowable claims in both applications, Applicants believe that the rejection may be overcome with a terminal disclaimer. Applicants respectfully defer a response until claims in each application are resolved.

REJECTION UNDER 35 U.S.C.§102

Claims 2-8, 11 and 13-32 have been rejected under 35 U.S.C.§102(b) as anticipated by the Ebert *et al.* reference. The reference purportedly teaches a specific GIP antiserum containing an antibody or antibodies that are antagonists of GIP and that are an "effective alternative to a referenced GIP sequence" (page 16 of the office action).

Applicants have carefully read the Ebert paper and fail to find any indication of source or preparation of the GIP antiserum. Applicants believe it is fair to assume that the antiserum is a polyclonal antiserum prepared by methods known even in 1982; *i.e.*, by injecting GIP into rats (?), and after a suitable amount of time to allow antibodies to develop, collecting the antiserum.

There are significant differences between the work disclosed by Ebert, *et al.* and Applicants' experiments. As set forth in the new set of claims, Applicants claim antibodies from identified amino acid sequences, *e.g.* SEQ ID NO:2, not from the full-length native GIP.

Applicants' specification teaches that antigens 7-30 GIP and 10-30 GIP have been isolated and shown to have GIP antagonist activity. The specification contemplates but does not demonstrate antibodies that specifically bind to antigens 7-30 GIP and 10-30 GIP but states that antibodies from the GIP antagonists (see page 7, line 30-31) may be obtained in a number of ways and used as GIP antagonists (line 24-25). The specification describes use of GIP, the hormone binding domain of GIP receptor, or "antigenic recombinant peptide fragments of either of those proteins" (line 30). There was at the time of the filing of the application a high level of knowledge in the art of antibodies and recognized that antibodies could be made against almost any protein. It would be routine to prepare antibodies to the 7-30 GIP and 10-30 GIP amino acid sequences disclosed in the present application.

Accordingly, Applicants' antibodies are different from the polyclonal serum mentioned by Ebert, *et al.* because they are prepared against specified antigens, not against full-length native GIP.

Claims 20-23 and 27-32 stand rejected under 35 U.S.C.§102(a) as anticipated by Gelling, *et al.* It is the examiner's position that the claims in the priority applications, 08/984,476 and provisional application 60/032,329 do not describe a GIP antagonist comprising

amino acids 16-30, 21-30, 31-44 or 7-9 of GIP so that the enumerated claims are not entitled to the benefit of the earlier filing date.

Applicants respectfully disagree that Gelling, *et al.* qualifies as prior art. The provisional application filed December 3, 1996 predates the April, 1997 publication date of the Gelling, *et al.* reference. Moreover, segments 1-42, 1-30, 7-30, 16-30, 10-30, 21-30, 31-44 are specifically mentioned and tested in applicants' provisional application, while the segment 7-9 is indicated as being of importance in antagonist activity (see page 7 in the provisional application).

Therefore, Gelling, *et al.* is not properly raised as prior art.

REJECTION UNDER U.S.C.§103

Claims 2, 9, and 10 are rejected under 35 U.S.C.§103(a) as unpatentable over Ebert, *et al.* in view of Avis and/or Turco. The Ebert reference is cited as teaching use of a GIP antiserum as an antagonist of GIP and useful as a lyophilized preparation. In combination with Avis, the Action asserts that biologics (hence the Ebert polyclonal compositions) can be stored dry, while Turce teaches reconstitution in physiologically appropriate media, *e.g.* saline.

As discussed above, Ebert's compositions are not the same as those claimed by Applicants. The expectation is that polyclonal serum prepared from GIP would be distinctly different because a different antigen is used to prepare the serum.

Accordingly, the use of standard Remington text pharmaceutical formulations does not render Applicant's antibody compositions obvious and is not properly combined with the Ebert, *et al.* reference. Nor is it obvious to make a GIP antagonist as taught by Ebert because Ebert does not teach the amino acid segment GIP antagonists described by Applicants.

CLAIM OBJECTIONS

Claim 10 has been objected to as being in improper dependent form. Applicants' have canceled this claim, thereby obviating this objection.

CONCLUSION

Applicant believes all formalities have been complied with and a complete response has been submitted. It is respectfully submitted that this application is now in condition for allowance. Should any issues remain or should the Examiner believe that a telephone conference with Applicant's attorney would be helpful in expediting prosecution of this application, the Examiner is invited to contact the undersigned at 617.439.4444.

Respectfully submitted,

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